

U.S. Patent No. 11,371,055
Petition for Post-Grant Review – PGR2023-00022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INARI AGRICULTURE, INC.
Petitioner,

v.

CORTEVA AGRISCIENCE LLC,
Patent Owner.

Case PGR2023-00022
Patent No. 11,371,055

PETITION FOR POST-GRANT REVIEW

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TABLE OF EXHIBITS

Exhibit ("Ex.")	Description
1001	U.S. Patent No. 11,371,055 ("055")
1002	File History of U.S. Patent No. 11,371,055
1003	Declaration of Dr. Aron Silverstone ("Silverstone")
1004	Corteva Agriscience – Technology Use Agreement (8/2022) (https://www.corteva.us/content/dam/dpagco/corteva/na/us/en/files/trait-stewardship/DOC-Corteva-Technology-Use-Agreement-WATERMARK-NONEXECUTABLE-COPY.pdf)
1005	Wright, T.R. et al., Robust crop resistance to broadleaf and grass herbicides provided by aryloxyalkanoate dioxygenase transgenes, PNAS 107 (47) 20240-20245 (11/23/2010) (https://doi.org/10.1073/pnas.1013154107)
1006	<i>Enlist™ Herbicide Tolerance and Soybean Symptomology - Get the Facts</i> (https://www.enlist.com/en/News/enlist-tolerance-soybean-symptomology.html) (7/13/2021)
1007	<i>Director's Blog: the latest from USPTO leadership: Increasing transparency, boosting competition, and supporting innovation can deliver better choices for farmers in the seed marketplace</i> (https://www.uspto.gov/blog/director/entry/increasing-transparency-boosting-competition-and) (3/7/2023)
1008	<i>Executive Order on Promoting Competition in the American Economy</i> (https://www.whitehouse.gov/briefing-room/presidential-actions/2021/07/09/executive-order-on-promoting-competition-in-the-american-economy/) (7/9/2021)
1009	U.S. Department of Agriculture: <i>More and Better Choices for Farmers: Promoting Fair Competition and Innovation in Seeds and Other Agricultural Inputs</i> , A report directed by President Biden's Executive Order Number 14036: "Promoting Competition in America's Economy"

	(https://www.ams.usda.gov/sites/default/files/media/SeedsReport.pdf) (3/2023)
1010	Declaration Under 37 C.F.R. §1.132 of Dr. Terry R. Wright (7/29/2021)
1011	Corteva Agriscience: Enlist 1 Herbicide Label (https://www.corteva.ca/content/dam/dpagco/corteva/na/ca/en/files/products/label/DF-Enlist-1-Herbicide-Label-English.pdf)
1012	Corteva Agriscience: Enlist Duo Herbicide Label (https://www.corteva.ca/content/dam/dpagco/corteva/na/ca/en/files/products/label/DF-Enlist-Duo-Herbicide-Label-English.pdf)
1013	Anjanappa, R.B. and Gruissem, W., 2021. Current progress and challenges in crop genetic transformation. <i>Journal of Plant Physiology</i> , 261, 153411.
1014	Herman, P.L., Behrens, M., Chakraborty, S., Chrastil, B.M., Barycki, J. and Weeks, D.P., 2005. A three-component dicamba O-demethylase from <i>Pseudomonas maltophilia</i> , strain DI-6: gene isolation, characterization, and heterologous expression. <i>Journal of Biological Chemistry</i> , 280(26), pp.24759-24767
1015	Chekan, Jonathan R, et al. "Molecular basis for enantioselective herbicide degradation imparted by aryloxyalkanoate dioxygenases in transgenic plants." <i>Proceedings of the National Academy of Sciences</i> 116.27 (2019): 13299-13304.
1016	Englander, S.W. and Mayne, L., 2014. The nature of protein folding pathways. <i>Proceedings of the National Academy of Sciences</i> , 111(45), pp.15873-15880.
1017	Gao SS, Naowarojna N, Cheng R, Liu X, Liu P. Recent Examples of α -Ketoglutarate-Dependent Mononuclear Non-Haem Iron Enzymes in Natural Product Biosyntheses. <i>Nat Prod Rep</i> . 2018 Aug. 15; 35(8): 792–837.
1018	Peach C, Velten J. Transgene expression variability (position effect) of CAT and GUS reporter genes driven by linked divergent T-DNA promoters. <i>Plant Mol Biol</i> . 1991;17(1):49-60.

1019	Hogan, D.A., Smith, S.R., Saari, E.A., McCracken, J. and Hausinger, R.P., 2000. Site-directed Mutagenesis of 2, 4-Dichlorophenoxyacetic Acid/ α -Ketoglutarate Dioxygenase: IDENTIFICATION OF RESIDUES INVOLVED IN METALLOCENTER FORMATION AND SUBSTRATE BINDING. <i>Journal of Biological Chemistry</i> , 275(17), pp.12400-12409.
1020	Müller, T.A., Zavodszky, M.I., Feig, M., Kuhn, L.A. and Hausinger, R.P., 2006. Structural basis for the enantiospecificities of R- and S-specific phenoxypropionate/ α -ketoglutarate dioxygenases. <i>Protein Science</i> , 15(6), pp.1356-1368.
1021	Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, Tunyasuvunakool K, Bates R, Židek A, Potapenko A, Bridgland A, Meyer C, Kohl SAA, Ballard AJ, Cowie A, Romera-Paredes B, Nikolov S, Jain R, Adler J, Back T, Petersen S, Reiman D, Clancy E, Zielinski M, Steinegger M, Pacholska M, Berghammer T, Bodenstein S, Silver D, Vinyals O, Senior AW, Kavukcuoglu K, Kohli P, Hassabis D. Highly accurate protein structure prediction with AlphaFold. <i>Nature</i> . 2021 Aug.;596(7873):583-589.
1022	Bagdonas, H., Fogarty, C.A., Fadda, E. and Agirre, J., 2021. The case for post-predictional modifications in the AlphaFold Protein Structure Database. <i>Nature Structural & Molecular Biology</i> , 28(11), pp.869-870.
1023	Müller, TA, Fleischmann, T, van der Meer, JR and Kohler, HPE, Purification and characterization of two enantioselective α -ketoglutarate-dependent dioxygenases, RdpA and SdpA, from <i>Sphingomonas herbicidovorans</i> MH. <i>Applied and environmental microbiology</i> , 2006. 72(7), pp.4853-4861.
1024	Prabakaran, S., Lippens, G., Steen, H. and Gunawardena, J., 2012. Post-translational modification: nature's escape from genetic imprisonment and the basis for dynamic information encoding. <i>Wiley Interdisciplinary Reviews: Systems Biology and Medicine</i> , 4(6), pp.565-583.

1025	Streber, W.R., Timmis, K.N. and Zenk, M.H., 1987. Analysis, cloning, and high-level expression of 2, 4-dichlorophenoxyacetate monooxygenase gene <i>tfdA</i> of <i>Alcaligenes eutrophus</i> JMP134. <i>Journal of Bacteriology</i> , 169(7), pp.2950-2955.
1026	Brannigan, J.A. and Wilkinson, A.J., 2002. Protein engineering 20 years on. <i>Nature Reviews Molecular Cell Biology</i> , 3(12), pp.964-970.
1027	Westendorf, A, Müller, RH, Babel, W, Purification and characterisation of the enantiospecific dioxygenases from <i>Delftia acidovorans</i> MC1 initiating the degradation of phenoxypropionate and phenoxyacetate herbicides. <i>Acta biotechnologica</i> , 2003. 23(1), pp.3-17.
1028	Levels of Protein Organization (https://comis.med.uvm.edu/VIC/coursefiles/MD540/MD540-Protein_Organization_10400_574581210/Protein-org/index.html)
1029	Corteva Agriscience Enlist Weed Control System 2020 Product Use Guide (https://www.enlist.com/content/dam/hdas/enlist/pdfs/Enlist_Product_Use_Guide_2020.pdf)
1030	NASA JPL, Genesis – Search for Origins, A Public Outreach Module: Atoms, Elements, and Isotopes (https://solarsystem.nasa.gov/genesismission/science/mod2_aei/index.html)
1031	Oxford University Press, Oxford Education Blog, Number of Atoms in the Universe (https://educationblog.oup.com/secondary/maths/numbers-of-atoms-in-the-universe)
1032	Declaration of Jonathan Bradford
1033	Nelson, D.L, and Cox, M.M., 2005. <i>Lehninger Principles of Biochemistry</i> , 4th edition, pp.116-156.

1034	Mall, T., Gupta, M., Dhadialla, T.S. and Rodrigo, S., 2019. Overview of biotechnology-derived herbicide tolerance and insect resistance traits in plant agriculture. Transgenic plants: methods and protocols, pp.313-342.
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I. INTRODUCTION

Petitioner Inari Agriculture, Inc. (“Petitioner”) respectfully requests Post-Grant Review (“PGR”) of claims 1-33 (“Challenged Claims”) of U.S. Patent No. 11,371,055 (“’055”) in accordance with §§321-329 and §42.200 et seq.¹

The ’055 patent is directed to transgenic plant cells expressing a recombinant Aryloxyalkanoate Dioxygenase (“AAD-12”), which enzyme purportedly degrades both phenoxy auxin herbicides and pyridyloxy auxin herbicides, thus conferring resistance thereto. *See* Ex. 1001, 7:63-9:10. The ’055 was allowed after Patent Owner argued an efficacy toward pyridyloxy auxin herbicides – but, the specification neither supports nor enables the scope of the issued claims.

Of course, enzymes degrading phenoxy auxin herbicides were previously known in the art. *See, e.g.*, Ex. 1010, ¶¶6, 8. As a result, to secure allowance of the ’055, Patent Owner stressed that its discovery “could impart commercial levels of resistance in planta, and not only to a phenoxy auxin herbicide but also to substrates (i.e. a pyridyloxy auxin herbicide), never previously tested...” Ex. 1002, 390 (emphasis in original). But this claimed function of the AAD-12 enzyme is

¹ Section cites are to 35 U.S.C. or 37 C.F.R. as context indicates, and all emphasis/annotations added unless noted.

simply not supported in the specification, and but for this representation the claims of this patent would never have issued. Indeed, Patent Owner warns its customers of exactly this fact. Patent Owner manufactures AAD-12 products (*e.g.*, under the “Enlist” label²) with materials that expressly prohibit broad use of phenoxy auxin herbicides and “pyridine auxin herbicides (*e.g.*, triclopyr, fluroxypyr)”:

In addition to the above Prohibited Activities, and with respect to Enlist® herbicides, Grower acknowledges and agrees that Grower is NOT permitted to do any of the following and should Grower, or someone on Grower's behalf, perform any of the activities listed below, shall result in Grower being in breach of this TUA:

- **following burndown, use any pyridine auxin herbicides (*e.g.*, triclopyr, fluroxypyr) on emerged Enlist® crops;**
- **following burndown, use any phenoxy auxin herbicide-containing product (*e.g.*, containing 2,4-D, 2,4-DB, MCPA, dichlorprop, LV6, MCPB, mecoprop, which is NOT expressly labeled for use in conjunction with Enlist crops, including pre-emergent use; and/or**
- **following burndown, use any AOPP herbicides (*e.g.*, quizalofop, cyhalofop, haloxyfop, diclofop, fenoxaprop, fluazifop) not expressly labeled for Enlist® corn on emerged Enlist corn;**

Ex. 1004, 2. PO's website is silent as to pyridyloxy auxin herbicide resistance—as it should be since it is related to a prohibited activity. *See* §§IX.A.2(a), IX.B.2(a).

The '055 patent was an improvidently granted patent. Its continued enforcement facilitates Patent Owner's unjust taxing of U.S farmers for a seed technology that was squarely in the public domain. This predatory behavior is now the focus of new government initiatives to ensure that the intellectual property

² *See* Ex. 1011, 6 (“Enlist E3 soybeans contain an AAD-12 expressing event. AAD-12 provides resistance to 2,4-D Choline Salt herbicides.”); Ex. 1012, 1 (“Enlist Duo Herbicide,” “Active Ingredient: 2,4-D, present as choline salt... glyphosate, present as dimethylamine salt”), 11 (“Enlist soybeans contain an AAD-12 expressing event plus a glyphosate tolerance trait. These are patented genes that provide tolerance to Enlist Duo Herbicide”).

system is not used to unnecessarily reduce competition in seed markets by enhancing the quality of patent examination.³ It is patents like this one that have caught the eye of the U.S. government. Accordingly, the claims should be cancelled as unpatentable as lacking necessary written description and enablement support in the specification.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner identifies Inari Agriculture, Inc. as real party-in-interest.

³ Ex. 1007 (USPTO Director’s Blog, recognizing that the “patent system must not be used to unnecessarily reduce competition beyond what is reasonably contemplated by the law” and calling to “enhance the quality of the patent examination process for innovations related to agricultural products and processes, including ... training and guidance to patent examiners”); Ex. 1008 (President Biden’s Executive Order on Promoting Competition, recognizing that “farmers are squeezed between concentrated market power in the agricultural input industries — seed, fertilizer, feed, and equipment suppliers — and concentrated market power in the channels for selling agricultural products” and recognizing the need “[t]o avoid the potential for anticompetitive extension of market power beyond the scope of granted patents”); Ex. 1009, 74-81 (USDA Report as Directed by the Executive Order, finding that, *e.g.*, much crop IP is owned by just one to four firms).

No other party had access to or control over the present Petition, and no other party funded or participated in preparation of the present Petition.

B. Related Matters

Petitioner is not aware of any matters related to the '055 patent.

C. Lead and Back-up Counsel, and Service Information

Lead Counsel	Backup Counsel
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III. PAYMENT OF FEES

The undersigned authorizes the Office to charge the fee required by §42.15(b) and any additional fees that might be due to Deposit Account No. 18-1945, under Order No. 118525-0001-008.

IV. REQUIREMENTS FOR POST-GRANT REVIEW

A. Grounds for Standing

Pursuant to 37 C.F.R. §42.204(a), Petitioner certifies that the '055 is available for PGR and that Petitioner is not barred or estopped from requesting PGR of the Challenged Claims of the '055 on the grounds identified herein. The '055 issued on 6/28/2022, and this Petition is being filed within nine months of that issue date (3/28/2023). *See also* §IV.B.1 below regarding eligibility for PGR.

B. Identification of Challenge

Pursuant to 37 C.F.R. §§42.204(b) and (b)(1), Petitioner requests PGR of the Challenged Claims and that the Board cancel the same as unpatentable. The '055 matured from U.S. Patent Application No. 15/468,494, filed 3/24/2017 (“’494 Application”). The '055 further claims priority to Application Nos. 14/491,197 (filed 9/19/2014; “’197 Application”), 13/647,081 (10/8/2012; “’081 Application”), 12/091,896 (10/27/2006; “’896 Application”), and 60/731,044 (filed 10/28/2005; “’044 Application”).

1. The '055 is Eligible for PGR

The '055 is eligible for PGR because it is entitled to a priority date no earlier than 3/24/2017 (the actual filing date of the '494 Application) and is therefore an AIA “first-to-file” patent filed on or after 3/16/2013. Although the '055 claims priority to several pre-AIA applications, the '055 claims include limitations that

both lack a proper written description and are not enabled, as explained in detail in §IX below. Such '055 claims failing to satisfy §112 based on the '055 specification or any other prior application (*i.e.*, the '197, '081, '896, and '044 Application specifications) are at best entitled to their own actual filing date of 3/24/2017. 35 U.S.C. §100(i)(1) states:

(1) The term “**effective filing date**” for a claimed invention in a patent or application for patent means—

(A) if subparagraph (B) does not apply, the actual filing date of the patent or the application for the patent containing a claim to the invention; or

(B) the filing date of the earliest application for which the patent or application is entitled, as to such invention, to a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b) or to the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c).

And because the '055 specification was amended during prosecution of the '494 Application,⁴ all the disclosures of the parent applications (to which the '055 claims to be continuations) are, *at best*, the same as the '055. Thus, because the

⁴ For the purposes of this PGR, Petitioner takes no position as to whether the matter added to the specification is “new matter,” as the '055 specification is deficient under §112 even with the addition.

'055 specification fails to support and/or enable the '055 claims, as explained in detail in §IX below, its parent applications also fail for the same reasons.

The effective filing date of the '055 is the actual filing date of the '055: 3/24/2017. The '055 is eligible for PGR.⁵

2. Statutory Grounds on Which the Challenge is Based

Petitioner respectfully requests cancelation of the Challenged Claims on the following grounds:

Ground	Statute	Claim(s)
1	§112(a) (enablement)	1-33
2	§112(a) (written description)	1-33

The information required by §§42.204(b)(4)-(5) is provided in Section IX.

⁵ See, e.g., *US Endodontics, LLC v. Gold Standard Instruments, LLC*, PGR2015-00019, Paper 54 at 6-12 (PTAB 12/28/2016) (finding PGR eligibility for patent issuing from transition application, holding that where “neither the [reviewed patent’s] application nor any of the earlier applications adequately supports [the] claims..., the effective filing date for those claims is the actual filing date”); *Schul Int’l Co., LLC v. Emseal Joints Sys., Ltd.*, PGR2018-00034, Paper 7 at 10-16 (PTAB 8/22/2018) (finding PGR eligibility for patent issuing from transition application, holding that “the [reviewed patent’s] disclosure fails to demonstrate possession” and “the effective filing date of the claimed inventions ... is the patent’s actual filing date”).

This Petition is supported by the Declaration of Dr. Aron Silverstone (Ex. 1003, ¶¶1-97) (“Silverstone”).

V. THE BOARD SHOULD NOT EXERCISE ITS DISCRETION TO DENY INSTITUTION

The Board should not exercise its discretion to deny institution under §§325(d) or 324(a).

A. §325(d)

Considering the two-part framework discussed in *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Pap. 6, *8-9, the Board should not exercise its §325(d) discretion to deny institution based on any enablement or written description arguments herein.

The §112 written description arguments in Ground 1 are not the same/substantially the same as arguments considered during prosecution. The *Advanced Bionics* inquiry ends at the first step. During prosecution of the ’055, the Examiner rejected the claims because Applicant amended the claims to recite an “AAD-12 motif,” which was not literally recited in the original specification. For example, Examiner argued, and repeated across three office actions, that:

Applicant does not describe the genus of AAD-12 proteins. The “AAD-12 motif” recited in the claims appears to be the specific motif in instant SEQ ID NO: 2 that represents the general motif found in α -ketoglutarate-dependent dioxygenases (paragraph 0053 on pages 12-13

of the instant Specification). Applicant does not describe a structural/functional relationship between the “AAD-12 motif” and enzymatically degrading a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. In particular, Applicant does not describe what specific features (amino acids) in the “AAD-12 motif” are critical to the recited function. [¶] Hence, it is unclear that Applicant was in possession of the invention as broadly claimed.

and that:

Applicant has failed to describe a representative number of species that would represent the variation within the claimed genus.

Ex. 1002, 213-214, 253-257, 314-317. The Examiner’s rejections were conclusory, as was the Examiner’s ultimate decision to withdraw the written description rejection. In fact, there is no indication as to any particular reason why the Examiner withdrew the rejection.

To the extent the Examiner’s rejections are considered the same as the written description arguments presented herein—although, based on the Examiner’s cursory analysis and conclusory statements alone, it cannot be said that the arguments are “the same”—the Examiner erred in withdrawing the written description rejection.

[illegible][illegible]

variations. There is simply no discussion of any species with less than 99.7 identity with SEQ ID NO: 2. *See* §IX.A.2(a) below.

And, while Applicant referenced alleged POSITA familiarity with the “family of α -ketoglutarate dioxygenases [as being] a well-studied class of enzymes” (Ex. 1002, 345-348), such familiarity does not account for the purported functionality of the claimed “AAD-12 motif” as being able to degrade both phenoxy and pyridyloxy auxin herbicides. No other members of α -ketoglutarate-dependent dioxygenases, which admittedly exhibit “a high level of unpredictability associated with expressing bacterial genes in plant systems,” are shown to exhibit the same claimed functionality of the “AAD-12 motif,” and Applicant alleged, with respect to nonobviousness, that it selected the AAD-12 protein with low homology to *tfdA*, against “[c]onventional wisdom.” Ex. 1002, 389-391; Ex. 1010, ¶¶9-10. Thus even if α -ketoglutarate-dependent dioxygenases have residues that could correspond to those identified in the claimed “AAD-12 motif,” such similarity in structure cannot serve to explain the functionality of the claimed genus because the α -ketoglutarate-dependent dioxygenases do not provide the same functionality of degrading both phenoxy and pyridyloxy auxin herbicides. *See* §IX.A.2(a) below.

Therefore, to the extent the Examiner withdrew the written description rejection because he believed a representative number of species are disclosed in

the '055, or because he believed that a common structure is disclosed in the '055, the withdrawal was in error. The claims requiring as little as 85% percent identity to SEQ ID NO: 2 to provide the claimed degradation functions are not supported by disclosure requiring 99.7% identity to SEQ ID NO: 2. And, the alleged structural commonality with the α -ketoglutarate dioxygenase family cannot fill gaps in the disclosure where the family itself does not provide the claimed degradation functions. The Board should not exercise its §325(d) discretion to deny institution based on the written description arguments herein.

Moreover, evidence not previously before the Examiner shows that the full claimed invention does not function to degrade both phenoxy and pyridyloxy auxin herbicides. PO's Use Agreements for Enlist Soybeans expressly prohibit the use of pyridine auxin herbicides—resistance is only provided against phenoxy auxin herbicides. *See* Ex. 1004, 2; Ex. 1011, 6; Ex. 1012, 1, 11. The '055 itself provides no indication of support for efficacy in soybeans or cotton. Patent Owner cannot have possessed the claimed invention, which does not actually function. *See* §IX.A.2(b) below. Therefore, in addition to the Examiner's error in withdrawing the written description rejection, Petitioner presents new evidence that shows Patent Owner did not possess the claimed invention, and the Board should not exercise its §325(d) discretion to deny institution based on the written description arguments herein.

The §112 enablement arguments in Ground 2 are not the same/substantially the same as arguments considered during prosecution. No rejections were made under §112 (enablement) during prosecution of the '055. The Examiner never argued that a POSITA would not be able to make and use the claimed invention, nor did the Examiner argue that undue experimentation would be required to make and use the claimed invention. The Examiner did not analyze the Wands factors. The Board should not exercise its §325(d) discretion to deny institution based on the enablement arguments herein. *See Lifescan Global Corp. v. Ikeda Food Research Co.*, PGR2019-00032, Paper 11 at 14 (declining to deny institution under §325(d) where enablement arguments presented in the petition were not previously considered “beyond the consideration given to all allowed claims for compliance with the requirements of 35 U.S.C. § 112,” also holding that “the mere absence of a rejection does not reflect that the Examiner already considered the specific arguments presented in the Petition”).

However, to the extent argued that the descriptions of written description during prosecution are, in fact, previously considered arguments directed to the enablement of the claims (factually, they are not), the Board should not exercise its §325(d) discretion to deny institution based on the enablement arguments herein. As discussed above, the Examiner withdrew the written description rejection in error and, moreover, did not have specific evidence before them showing that the

claimed invention does not work—as even Patent Owner admits to its customers.

The same new evidence speaking to the non-functionality of the claimed invention also speaks to the enablement of the claims.

Additionally, the enablement rejection below includes a detailed analysis of the Wands factors that speak to the amount of experimentation required to practice the full scope of the claimed invention, which the Examiner is not in the best position to ascertain, including (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Examiner never considered how a POSITA would practice the claimed invention or, consequently, the amount of undue experimentation that a POSITA would require to practice the claimed invention. For example, the Examiner never considered how a POSITA would have practiced the invention with respect to *in vitro* and *in vivo* testing, with respect to the sheer amount of testing required for the variety of the 2.4×10^{106} amino acid sequences that fall within the claims, or with respect to the species of plants claimed but that have no expectation of functioning as claimed (*e.g.*, transgenic soybean plants). See §IX.B.2 below. The Examiner also did not have before him the Declaration of Dr. Aron Silverstone (Ex. 1003), which describes,

inter alia, the state of the prior art and its highly unpredictable nature. Ex. 1003, ¶¶56-93. As the Examiner did not specifically consider how a POSITA would practice the invention or the undue experimentation such practice would require, the Board should not exercise its §325(d) discretion to deny institution based on the enablement arguments herein.

Furthermore, the claim limitations at issue herein are unique to the '055 patent and are not found in any of the '055's parent or child applications. Accordingly, no arguments regarding written description or enablement are revisited here. The Board should not exercise its discretion to deny institution under §325(d).

B. §324(a)

There is no co-pending litigation involving the '055 that would warrant discretionary denial of this Petition based the factors in *Apple Inc. v. Fintiv, Inc.* IPR2020-00019, Pap. 11.

VI. BACKGROUND

A. Summary of the '055 Patent

The '055 is directed to transgenic plant cells expressing a recombinant Aryloxyalkanoate Dioxygenase (“AAD-12”), which enzyme purportedly degrades both phenoxy auxin herbicides and pyridyloxy auxin herbicides, thus conferring resistance thereto. *See* Ex. 1001, 7:63-9:10.

AAD-12 is purported to catalyze reactions of the general form shown in FIG. 1 below, based on the reaction catalyzed by the homologous α -ketoglutarate-dependent 2,4-dichlorophenoxyacetate dioxygenase (“tfdA”), which has been used in transgenic plants to impart resistance to 2,4-D, a phenoxy auxin herbicide. See *id.*, Fig. 1, 3:10-21, 6:46-55, 10:65-11:1.

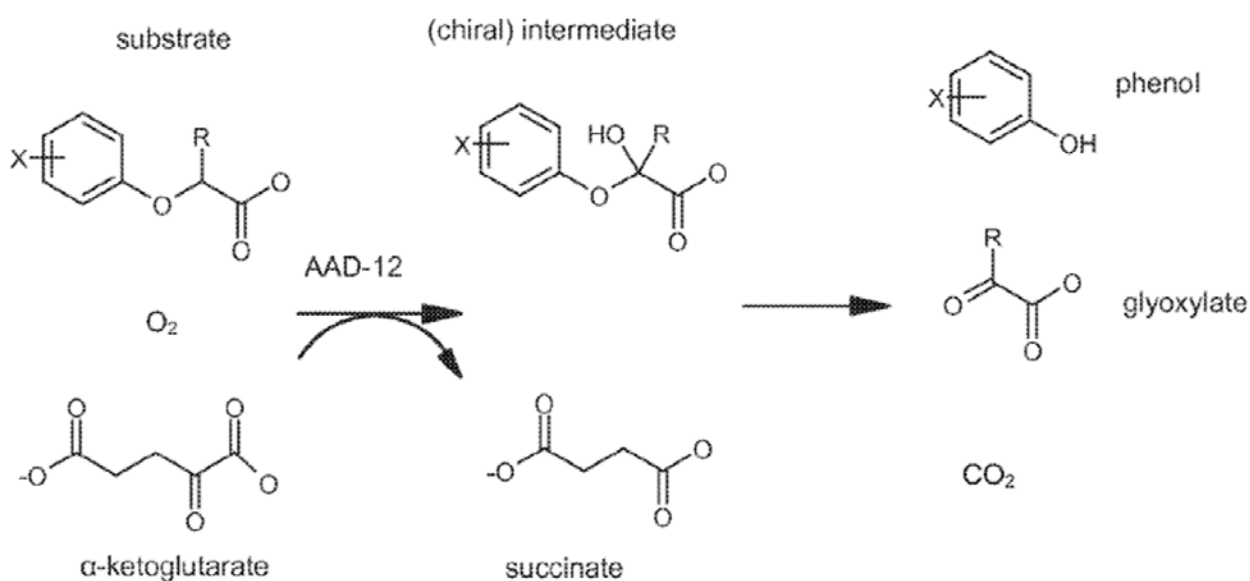


FIG. 1

The '055 claims that, unlike tfdA and other homologues, AAD-12 (SEQ ID NO: 2) has the unique ability to catalyze the degradation of both phenoxy auxin herbicides (including 2,4-D) and pyridyloxy auxin herbicides. *Id.*, 11:23-25. Per the '055, AAD-12 can thus confer resistance to a wide array of herbicides in

transgenic plants, allowing for cultivated plants compatible with broader and more robust weed control and herbicide resistance management options. *See id.*, 4:7-16.

The claims of the '055 are directed to transgenic plants comprising a recombinant polynucleotide encoding an AAD-12 protein with at least 85% sequence identity with SEQ ID NO: 2 and a conserved $\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{H}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$ motif, which AAD-12 protein enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. *Id.*, Cl. 1. Representative independent claim 1 of the '055 recites:

1. A transgenic plant cell comprising a recombinant polynucleotide that encodes an **AAD-12 protein** that exhibits aryloxyalkanoate dioxygenase activity **wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide**, further wherein said AAD-12 protein comprises:

i) an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2; and

ii) an AAD-12 motif having the general formula of:

$\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{T}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$, wherein

X_{109} represents a single amino acid at position 109, relative to the sequence of SEQ ID NO: 2;

$(\text{X})_{111-134}$ represents a sequence of 24 amino acids;

$(\text{X})_{136-261}$ represents a sequence of 126 amino acids; and

$(\text{X})_{263-272}$ represents a sequence of 10 amino acids.

Id. (emphasis added). Independent claim 32 adds only that the conserved AAD-12 motif has 90% sequence identity with positions 108-273 of SEQ ID NO: 2. *Id.*, Cl. 32. Independent claim 33 recites a method of controlling at least one weed in a field, wherein said field has been planted with transgenic seeds as recited in claim 1. *See id.*, Cls. 1, 33.

B. Prosecution History of the '055

U.S. Application 15/468,494, which matured into the '055 patent, was filed 03/24/2017 with sequence listings and 20 claims. Ex. 1002, 1-195.

Applicant included in their initial filing, on 03/24/2017, a Preliminary Amendment which cancelled original claims 1-26 and introduced new claims 27-58, directed to transgenic plants comprising a recombinant polynucleotide encoding an AAD-12 protein with at least 85% sequence identity with SEQ ID NO: 2 and a conserved “AAD-12 motif” of the form $HX_{109}D(X)_{111-134}H(X)_{136-261}H(X)_{263-272}R$, which AAD-12 protein enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide, and methods of use thereof. *Id.*, 151-158.

Examiner issued a Non-Final Office Action on 04/24/2019, rejecting claims 27-58 as failing to comply with the written description requirement, indicating that Applicant did not describe the claimed genus of AAD-12, as the “AAD-12 motif” recited in the claims was not disclosed in the specification and seemingly

represented the general motif found in α -ketoglutarate-dependent dioxygenases, and further that the Applicant did not describe a structural or functional relationship between the “AAD-12 motif” and enzymatic degradation of a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. *Id.*, 210-214. Examiner also rejected claims 27-58 under obviousness-type double patenting, and rejected claims 27-39, 41-54, and 57-58 as obvious over combinations of Kaphammer (U.S. 5,608,147), Schleinitz (*Appl. Environ. Microbiol.* 70(9):5357-5365), and Pallett (U.S. 7,205,561). *Id.*, 214-218.

Applicant, on 09/24/2019, filed an amendment to the specification to address the written description rejection, amending paragraph [0054] to add a disclosure of the “AAD-12 motif” as recited in the claims, and replacing Tables 1, 25, 26, and 26A to remove shading. *Id.*, 228-232. Applicant purported that the “AAD-12 motif” was consistent with the previously disclosed α -ketoglutarate-dependent dioxygenase motif as mapped onto SEQ ID NO: 2 or 4, and thus the amendment introduced no new matter. *Id.*, 238-239. Applicant argued that the two species of AAD-12 provided in the specification, coupled with the α -ketoglutarate-dependent dioxygenase motif provided a roadmap by which POSITAs may identify the claimed “AAD-12 motif”, and further that the specification provided a structural definition of the genus sufficient to meet the written description requirement; namely, the requirements that members of the genus have $\geq 85\%$ sequence identity

to SEQ ID NO: 2, the “AAD-12 motif”, and enzymatic activity for degrading phenoxy auxin herbicides as well as pyridyloxy auxin herbicides. *Id.*, 240-241.

Applicant further argued that the applied prior art did not render obvious the claimed sequence due to the low homology of AAD-12 to α -ketoglutarate-dependent dioxygenases known in the art to degrade herbicides. *Id.*, 242-243.

Examiner issued a Final Office Action on 12/20/2019, maintaining the rejections of claims 27-58. *Id.*, 251-264. Regarding the written description requirement, Examiner stated that the “description of a general structure known in an enzyme family does not adequately describe the specific structure required to produce activity that enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide” and that “Applicant fails to adequately describe the variation within the claimed genus, and Applicant has only described a very limited number of species that would fall within the claimed genus.” *Id.*, 256.

Applicant, on 04/17/2020, filed a Request for Continued Examination (“RCE”), merging claims 55 and 56, and adding new claim 59 directed to a transgenic plant comprising a recombinant polynucleotide that encodes an AAD-12 protein with an amino acid sequence 90% identical to amino acids 108-273 of SEQ ID NO: 2. *Id.*, 267-275. Regarding the written description requirement, Applicant argued that the disclosure provided sufficient written description for the claimed genus consistent with the March 25, 2008 revised written description training

materials, and that the functional definition of the genus as having the ability to enzymatically degrade phenoxy auxin herbicides as well as pyridyloxy auxin herbicides sufficiently defined the genus. *Id.*, 276-284.

Examiner issued a Non-Final Office Action on July 24, 2020, maintaining the rejections of claims 27-58. *Id.*, 312-326.

Applicant, on 01/21/2021, filed amendments to clarify the scope of claim 28 and fix the formats of claims 30, 49, 50, and 54. *Id.*, 336-342. Regarding the written description requirement, Applicant argued that the written description rejection should be withdrawn in view of the disclosure of the common structure of AAD-12, supported by the high level of background knowledge in the art relating to α -ketoglutarate-dependent dioxygenases and herbicide resistance. *Id.*, 342-348.

Examiner issued a Final Office Action on 05/03/2021, withdrawing the rejection of claims 27-58 as failing to satisfy the written description requirement in view of Applicant's remarks, but rejecting claims 30 and 54 as indefinite due to lack of proper antecedent basis and maintaining the rejection of claims 27-39, 41-54, and 57-59 as obvious over combinations of Kaphammer, Schleinitz, and Pallett. *Id.*, 353-364.

Applicant, on 08/03/2021, filed a Request for Continued Examination ("RCE"), amending claims 30 and 54 to overcome the indefiniteness rejection. *Id.*, 381-388. Applicant argued against the obviousness rejection of claims 27-39, 41-

54, and 57-59, stating that a POSITA would have had no motivation to combine the cited references, and further that a POSITA would have had no reasonable expectation of success in doing so. *Id.*, 389-393. Applicant relied upon its own inventor's declaration to support its argument, which declared, *inter alia*, that “[t]hose skilled in the art appreciate that there is a high level of unpredictability associated with expressing bacterial genes in plant systems,” such as between “two *tfdA* homologs” AAD-1 and AAD-2, which further expressed “surprising[]” *in vitro* vs *in vivo* activity. *Id.*, 376-380 (also provided separately as Ex. 1010, see ¶¶9-10 therein).

Examiner issued a Non-Final Office Action on 09/03/2021, withdrawing the rejections of claims 30 and 54 as indefinite and claims 27-39, 41-54, and 57-59 as obvious, but maintaining the rejection of claims 27-55 and 57-60 under obviousness-type double patenting. *Id.*, 394-399.

Applicant, on 12/02/2021, filed a Terminal Disclaimer to obviate the obviousness-type double patenting rejection. *Id.*, 483-484.

Examiner issued a Notice of Allowance on 03/01/2022. *Id.*, 485-491.

VII. LEVEL OF ORDINARY SKILL IN THE ART

The level of ordinary skill in the art is evidenced by the prior art. *See In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (determining that the Board did not err in adopting the approach that the level of skill in the art was best

determined by references of record). The prior art discussed herein, and in the declaration of Dr. Aron Silverstone, demonstrates that a POSITA, at the time the '055 was filed, had a Ph.D. in biochemistry, cell biology, genetics, or a related field, and 3-5 years of experience in the design or development of transgenic plants including genomics, proteomics, biochemistry, plant transformation and crop science, or the equivalent. Additional graduate education could substitute for professional experience, or significant experience in the field could substitute for formal education. Silverstone, ¶¶16-18.

VIII. CLAIM CONSTRUCTION

Claim terms subject to PGR are to be “construed using the same claim construction standard that would be used to construe the claim in a civil action under §282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” §42.200(b). Only terms necessary to resolve the controversy need to be construed, and should be given their plain and ordinary meaning. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).⁶

⁶ See generally *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005); 37

IX. GROUNDS OF UNPATENTABILITY

Although the '055 patent claims transgenic plants comprising a recombinant polynucleotide encoding an AAD-12 protein that exhibits the ability to enzymatically degrade **both** a phenoxy auxin herbicide and a pyridyloxy auxin herbicide, the Challenged Claims are invalid for failing to comply with the written description requirement, as Patent Owner disclosed a minimal structural definition, as well as a mere single example, of the claimed genus which covers up to 2.4×10^{106} species. *See* '055, Cl. 1; *see also* Silverstone, ¶¶80. Because the claimed genus reflects an enormous degree of structural diversity in terms of both protein sequence and tertiary structure, the disclosure of two species separated by a single alanine far removed from the “AAD-12 motif” is insufficient. Silverstone, ¶¶41-55. The '055 patent also fails to enable a POSITA to make and use a transgenic plant with properties of degrading **both** a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. Silverstone, ¶¶56-93. Further, Patent Owner explicitly discourages the use of pyridyloxy auxin herbicides with transgenic plants of the invention with every sold product, noting that transgenic plants of the invention do not in fact

C.F.R. §42.200(b). This claim-construction analysis is not a concession as to the scope of any claim term in litigation, or a waiver of any argument in any proceeding that claim terms are indefinite, invalid, or unpatentable.

exhibit increased resistance to pyridyloxy auxin herbicides. *See* Ex. 1004, 2; *see also* Silverstone, ¶54.

A. Ground 1: Claims 1-33 are Invalid for Failing to Meet the Written Description Requirement Under § 112(a)

1. Legal Standard for Written Description

35 U.S.C. § 112(a) requires that a patent specification

shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, ...

To satisfy the written description requirement, an application must “reasonably convey [] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*). In the case of “genus claims that use functional language to define the boundaries of a claimed genus . . . the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus.” *Id.*, 1349.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical

properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. *See Regents of the Univ. of Cal. v. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Satisfactory disclosure of a “representative number” depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, disclosure of a single species within a genus which embraces widely variant species has been found to be insufficient to support written description of the genus. *See id.*, 1568. Instead, the disclosure must adequately reflect the structural diversity of the claimed genus, either through the disclosure of sufficient species that are “representative of the full variety or scope of the genus,” or by the establishment of “a reasonable structure-function correlation.” Such correlations may be established “by the inventor as described in the specification,” or they may be “known in the art at the time of the filing date.” *See AbbVie Deutschland GmbH & Co., KG v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-01 (Fed. Cir. 2014).

As aforementioned, the disclosure must adequately reflect the structural diversity of the claimed genus. *Regents*, 119 F.3d, 1568. The claimed genus of

transgenic plants, comprising an AAD-12 protein with the ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides, lacks written description support because the specification describes only two species, 99.7% identical to one another, within a genus covering up to 2.4×10^{106} species, and further fails to establish a reasonable structure-function correlation between at least 85% sequence identity to SEQ ID NO: 2 and the “AAD-12 motif”, and the ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶¶41-55.

2. The '055 Patent Provides Insufficient Written Description Support for the Claimed Genus

The claims of the '055 patent are overly broad and functionally defined, and the specification fails to disclose either a representative number of species commensurate with the scope of the claim or establish a reasonable structure-function correlation. Silverstone, ¶¶41-55. Independent claim 1 recites a transgenic plant cell comprising a recombinant polynucleotide encoding an AAD-12 protein that 1) enzymatically degrades both a phenoxy and a pyridyloxy auxin herbicide, 2) has an amino acid sequence at least 85% identical to SEQ ID NO: 2, and 3) has an “AAD-12 motif” of $\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{T}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$. Ex. 1001, Cl. 1.

The claimed genus encompasses up to 2.4×10^{106} species, as discussed below, yet the specification discloses only two species, and tests only one, that

meet the structural requirements of the claims and possess the required functional features; the native AAD-12, and an AAD-12 variant that differs only by the addition of a single alanine residue near the N-terminus of the protein, 99.7% identical to the native AAD-12. Ex. 1001, SEQ ID NOS: 2, 4; Silverstone, ¶80, fn. 1. These working examples fall far short of the claims, which allow up to 43 mutations, including in the recited “AAD-12 motif” structure. *Id.* The ’055 patent provides no information, testing, data, or discussion of species with less than 99.7% sequence identity to SEQ ID NO: 2. *Id.*, ¶¶80-82.

And, given the unpredictable nature of protein folding and structure/function correlation, as discussed below, the minimal disclosure of the ’055 patent’s two species with 99.7% sequence identity fails to provide a representative number of species for the claimed genus, which embraces widely variant species. Silverstone, ¶¶42-50; *Regents*, 119 F.3d, 1568.

Aside from the requirement that AAD-12 proteins of the invention have at least 85% identity to SEQ ID NO: 2, the only structural definition of the genus disclosed was the five conserved residues of the 166 amino acid long “AAD-12 motif” and the lengths of amino acid sequences around and between them. Ex. 1001, Cl. 1, Silverstone, ¶79. And although the genus is functionally defined to include only those sequences exhibiting “aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a

pyridyloxy auxin herbicide,” no clear link between the recited “AAD-12” motif and the novel ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides is disclosed. Silverstone, ¶¶42-50, 79. Indeed, the defined residues of the “AAD-12 motif” are conserved in, for example tfDa as well, yet it does not exhibit claimed functionality. Ex. 1001, Fig. 2. And the chain lengths (around and between the conserved residues of the “AAD-12 motif”) alone cannot confer this functionality on a protein; the function of a protein is dependent on its folded, tertiary structure, which depends far more on amino acid sequence than on sequence length. Silverstone, ¶¶42-50. Patent Owner failed to show the creation of a generic invention that achieves the claimed result, as seen in the single working example disclosed.

Because the function of a protein is dependent on its folded, tertiary structure, and because five isolated residues of a protein and the lengths of sequences between them are insufficient to impart said tertiary structure, more is needed to establish “a reasonable structure-function correlation.” *AbbVie*, 759 F.3d, 1300-01; Silverstone, ¶¶42-50. Claims 1-33 are, therefore, unpatentable for failing to satisfy the written description requirement under § 112(a). Silverstone, ¶¶41-55.

(a) **There is no Written Description Support for AAD-12 Proteins Having Less Than 99.7% Identity to SEQ ID NO: 2**

The '055 patent discloses two species, native AAD-12 and the AAD-12 variant, the only species tested, to which are attributed aryloxyalkanoate dioxygenase activity for the degradation of both phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶80. These species, with 99.7% sequence identity, differ by the insertion of a single alanine at the N-terminus of the protein, 107 amino acids removed from the “AAD-12 motif” and not indicated to have any significant affect upon the tertiary structure of the protein. Ex. 1001, 35:8-13; Silverstone, ¶80. Such a negligible degree of variation between proteins exhibiting the claimed functionality is not informative as to the structural features necessary to impart the claimed functionality to proteins. Silverstone, ¶¶42-50. Yet, as discussed below, the claimed genus covers up to 2.4×10^{106} species⁷ with as little as 85% sequence identity to SEQ ID NO: 2. Ex. 1001, Cl. 1; Silverstone, ¶80, fn. 1. The claims place no limits on the types of mutations that can be made, or where in the sequence they

⁷ The number of atoms in a *gold coin* may approximate 10^{22} . See Ex. 1030, 3. The number of atoms in our *solar system* has been approximated at 10^{56} —an increase by a factor of 34. See Ex. 1031, 2. The number of atoms in the *universe* has been approximated at 10^{80} —an increase of the already large number by a factor of 13. *Id.* The '055 patent's number of claimed species **exceeds** even the universe by a factor of **26**. This number is unfathomably large.

can be made, aside from the 5 conserved amino acids of the “AAD-12 motif” and the chain lengths around and between them. Silverstone, ¶79.

The final three-dimensional (“tertiary”) structure of a protein is critical for its function and is determined by factors including, but not limited to, the pH, salinity, and temperature of the surrounding environment, the presence and identity of chaperone proteins involved, and post-translational modifications. Silverstone, ¶¶42-43. The tertiary structure of a protein cannot be accurately predicted solely from the primary amino acid sequence. Silverstone, ¶¶42-47. Furthermore, enzymes, such as AAD-12, require a specific spatial arrangement of amino acids to form the active site, which is responsible for the chemical reaction catalyzed by the enzyme. Silverstone, ¶42. Anything that alters or impacts the shape of the active site of an enzyme can have significant effects on the substrate specificity, catalytic activity, and other biochemical parameters thereof, or abrogate activity altogether. Silverstone, ¶43.

Because the '055 patent does not disclose any species with less than 99.7% sequence identity to SEQ ID NO: 2, it does not provide any direction or guidance as to species with any greater degree of variation than that. Protein folding and activity is a largely unpredictable field of study, relying on trial and error as our ability to accurately predict slowly improves. Silverstone, ¶42. As discussed above, for inventions in an unpredictable art, disclosure of a single species within a genus

which embraces widely variant species has been found to be insufficient to support written description of the genus. *Regents*, 119 F.3d, 1568. The disclosure of the '055 patent, which provides only two, nearly identical species of a genus encompassing up to 2.4×10^{106} species, fails to satisfy this requirement. Silverstone, ¶80, fn. 1.

The '055 patent also fails to describe a reasonable structure-function correlation between at least 85% sequence identity to SEQ ID NO: 2 and the “AAD-12 motif”, and the ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶¶48-50. Enzyme function is largely a product of the tertiary structure of the protein, which forms the 3-dimensional (“3-D”) structure of the enzyme as a whole and its critical active site. Silverstone, ¶¶42-43. Anything that alters the shape of an enzyme’s active site can impact the substrate specificity of the enzyme, and impact, or even abrogate entirely, its function. Silverstone, ¶¶43-44.

The five conserved residues of the “AAD-12 motif” correspond to key active site residues of homologous members of the family of α -ketoglutarate-dependent dioxygenases, as seen in sequence alignment provided in the '055 patent. Ex. 1001, Fig. 2; Silverstone, ¶48. Yet no other members of the family of α -ketoglutarate-dependent dioxygenases have been shown to exhibit the claimed functionality; thus the maintenance of these active site residues alone cannot explain the novel

functionality of the claimed genus. Silverstone, ¶48. While the conserved amino acids of the “AAD-12 motif” are necessary for the claimed activity, they are not sufficient to determine substrate specificity or activity—that depends on those amino acids (and indeed the rest of the amino acids forming the active site) being positioned in the correct spatial configuration. Silverstone, ¶¶48-49.

The function of AAD-12 proteins of the invention depends on the correct 3-D structure of the active site (to correctly position these conserved active site residues), and the correlation between protein primary structure (amino acid sequence) and tertiary structure (folded globular protein) remains difficult to predict, even if advanced protein prediction software were available. Silverstone, ¶¶46-47. It would be nearly impossible for a POSITA to predict whether a species other than the disclosed AAD-12 or AAD-12 variant would function as claimed from the disclosure of the '055 patent, even in view of the state of the art at the time of filing.⁸ Silverstone, ¶¶48-50.

The activity and substrate specificity of an amino acid sequence within the scope of the claims, other than the disclosed AAD-12 or AAD-12 variant, could only be accurately determined by meticulous *in vitro* testing; the '055 patent, as

⁸ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9.

described above, does not provide sufficient disclosure to support any correlation between the claimed structural elements and the ability to degrade both phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶¶42-50. Absent such correlation or any indication that the corresponding key active site residues of the family of α -ketoglutarate-dependent dioxygenases exhibits the claimed functionality, for example, Patent Owner has failed to disclose “a reasonable structure-function correlation” for the claimed genus and has failed to disclose “species sufficient to support a claim to the functionally-defined genus.” *Ariad*, 598 F.3d, 1349. Thus, Patent Owner has failed to satisfy the written description requirement under § 112(a).

(b) The Two Species Disclosed in the '055 Patent do not Function as Claimed Across the Genus of Transgenic Plants

Patent Owner cannot reasonably convey possession of the claimed subject matter because, as Petitioner’s experiments evidence demonstrate, and Patent Owner’s own publications show, the claimed invention does not function. *See supra*; Ex. 1004, 2; *see also* Silverstone, ¶¶51-55. For example, the specification provides experimental results for seven species of plants comprising the AAD-12 variant, with some, but not all, of the tested plant species showing herbicide resistance to both phenoxy and pyridyloxy auxin herbicides. Ex. 1001, 48:62-102:49. Yet no data is presented for the herbicide resistance of transgenic soybeans

comprising the AAD-12 variant against pyridyloxy auxin herbicides. Ex. 1001, 31:55-102:49; Silverstone, ¶53. Further, no data is presented for the herbicide resistance of transgenic cotton comprising the AAD-12 variant against any herbicides; the data concerns transformation efficiency, and provides only prophetic experiments to test for phenoxy, but not pyridyloxy, auxin herbicide resistance. Ex. 1001, 80:62-82:26; Silverstone, ¶53.

In fact, Patent Owner’s own Technology Use Agreement (the “Agreement”) for Pioneer® Brand Enlist E3 Soybeans—transgenic soybeans comprising the AAD-12 variant—expressly prohibits use, following burndown, of “any pyridine auxin herbicides (e.g., tirclopyr, fluroxypyr) on emerged Enlist crop[.]” Ex. 1004, 2; Silverstone, ¶54. The Agreement, the ’055 patent, and indeed Patent Owner’s marketing materials, make clear that transgenic soybeans comprising the AAD-12 variant show herbicide resistance only to phenoxy auxin herbicides such as 2,4-D. *See supra*; Silverstone, ¶¶53-54; Ex. 1004, 2; Ex. 1006; Ex. 1011, 6 (“AAD-12 provides resistance to 2,4-D Choline Salt herbicides.”); Ex. 1012, 1 (“Enlist Duo Herbicide,” “Active Ingredient: 2,4-D, present as choline salt... glyphosate, present as dimethylamine salt”), 11 (“Enlist soybeans contain an AAD-12 expressing event plus a glyphosate tolerance trait. These are patented genes that provide tolerance to Enlist Duo Herbicide”). The species of AAD-12 protein disclosed and used by Patent Owner, one of only two species that allegedly support

the claimed genus, fails to “exhibit[] aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide” in at least one transgenic plant cell explicitly tested in the disclosure. Ex. 1001, Cl. 1. Patent Owner has failed to show possession of the invention as claimed, and thus cannot have satisfied the written description requirement under § 112(a).

B. Ground 2: Claims 1-33 are Invalid for Failing to Meet the Enablement Requirement Under § 112(a)

1. Legal Standard for Enablement

Section 112(a) contains an enablement requirement separate from the written description requirement. *See Ariad*, 598 F.3d, 1344. To satisfy the enablement requirement of §112(a), “the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without “undue experimentation.” *Genentech Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). “Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation.” *Wyeth & Cordis Corps. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). “It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.” *Genentech*, 108 F.3d, 1366.

Undue experimentation factors include “(1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.” *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). These factors are merely illustrative; an individual case must turn on its facts. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). “A patentee who chooses broad claim language must make sure the broad claims are fully enabled.” *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008).

“[T]he enablement inquiry for claims that include functional requirements can be particularly focused on the breadth of those requirements, especially where predictability and guidance fall short. In particular, it is important to consider the quantity of experimentation that would be required to make and use, not only the limited number of embodiments that the patent discloses, but also the full scope of the claim.” *Amgen Inc. v. Sanofi*, 987 F.3d 1080, 1086 (Fed. Cir. 2021) (*cert. granted*).

In the present case, claims 1-33 are invalid for failing to comply with the enablement requirement. The relevant *Wands* factors all demonstrate that undue experimentation would be required to practice the full scope of the claimed

invention, rendering the claims invalid for lack of enablement under 35 U.S.C. § 112(a).

While the current standard for enablement (specifically, undue experimentation) is being considered by the Supreme Court, the claims here fail even under a more permissive standard. In *Amgen*, the patent disclosed twenty-six amino acid sequences of the claimed invention of “millions of antibody candidates within the scope of the claims,” along with a roadmap to make and test proteins for the claimed functionality. *Amgen*, 987 F.3d, 1085-86. These twenty-six antibodies represent various antigen-binding site sequences and structures that accomplish the claimed functionality, and the Supreme Court could find such disclosure to be sufficiently enabling so as to not require undue experimentation. *Id.* Even if this is found to be an enabling disclosure at the Supreme Court, the '055 specification is too far removed from any reasonable level of disclosure and is not a reasonable analog to the *Amgen* fact pattern. Patent Owners here disclosed only two sequences, differing by a single amino acid at the N-terminus of the sequence, of up to 2.4×10^{106} species within the scope of the claim. Thus the '055 patent discloses **one order of magnitude** fewer embodiments for a genus approximately **one hundred orders of magnitude** larger in size. Even under a more permissive standard, the experimentation required to make and use the full scope of the claims of the '055 patent would be undue.

2. Wands Factor Analysis

(a) Extensive and Undue Experimentation is Required to Practice the Full Scope of the Claimed Invention

Reaching the full scope of claims 1-33 requires an extensive amount of experimentation to test for aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide across the broad range of amino acid sequences having at least 85% sequence identity with SEQ ID NO: 2, and an AAD-12 motif having the general formula of: $\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{T}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$, and further across the broad range of transgenic plants comprising those amino acid sequences. *See* Ex. 1001, Cls. 1, 32, 33; *see also* Silverstone, ¶¶57, 86-93.

Reaching the full scope of the claims of the '055 patent would require the testing of all proteins comprising an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2 and an AAD-12 motif having the general formula of: $\text{HX}_{109}\text{D}(\text{X})_{111-134}\text{T}(\text{X})_{136-261}\text{H}(\text{X})_{263-272}\text{R}$ to determine whether they had aryloxyalkanoate dioxygenase activity as claimed. *See* Ex. 1001, Cl. 1. Because SEQ ID NO: 2, is 292 amino acids in length, a protein comprising an amino acid sequence having at least 85% sequence identity with SEQ ID NO: 2 can include up to 43 mutations. *See* Ex. 1001, 109-110; *see also* Silverstone, ¶80, fn. 1. Even limiting the genus to proteins having 90% sequence identity with SEQ ID NO: 2, as in claims 2 and, in part, 32 of the '055 patent allows for up to 29 mutations. *See*

id. For each of the mutations, at least 19 potential substitutions can be made (accounting for the 20 canonical amino acids), in addition to the insertion or deletion of an amino acid. *Id.* And because the claimed “AAD-12 motif” comprises only 5 conserved amino acids, the mutations may be made at any of 286 positions in the sequence, accounting for the “start” codon encoding methionine. *See* Ex. 1001, Cl. 1; *see also* Silverstone, ¶80, fn. 1. The broad claim allows for up to 2.4×10^{106} amino acid sequences that fall within the claims but without any meaningful disclosure as to whether or why such would in fact work. Silverstone, ¶¶80-82, fn. 1. Given that the ’055 patent only structurally defines the genus based on 85% sequence identity to SEQ ID NO: 2 and the presence of the “AAD-12 motif,” it would be nearly impossible to reliably predict whether any other sequence within the scope of the claim would work.⁹ Ex. 1001, Cl. 1; Silverstone, ¶¶78-79.

Due to the functional limitation of the claims, namely, that an AAD-12 protein of the invention “exhibits aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide,” each amino acid sequence (as discussed above) would have to be experimentally analyzed *in vitro* for its ability to enzymatically degrade a phenoxy

⁹ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9.

auxin herbicide and a pyridyloxy auxin herbicide. Ex. 1001, Cls. 1, 32, 33. This experimental analysis would require 1) cloning and construction of an expression vector, 2) transformation and culturing of host cell for expression, 3) extraction and purification of expressed protein, and 4) *in vitro* analysis of aryloxyalkanoate dioxygenase activity of purified variant AAD-12 protein. Silverstone, ¶¶89-90. Such experimental analysis would be required for any amino acid sequence falling within the claims that differed from the native AAD-12 (SEQ ID NO:2) and the AAD-12 variant tested (SEQ ID NO:4). Silverstone, ¶¶89-90. Given the universe of species that fall within the genus, this testing would be exceedingly time-consuming, laborious, expensive, and unpredictable. Silverstone, ¶¶86-90. Moreover, even the identification of species exhibiting the desired enzymatic activity could not reliably predict whether that enzymatic activity would be maintained in transgenic plants of interest. Silverstone, ¶91.

The abovementioned experimental analysis for enzyme activity, however, would only be a starting point for reaching the full scope of the claims of the '055 patent. Because translation of *in vitro* expression and activity to *in vivo* expression and activity is unpredictable, each amino acid sequence found functional via *in vitro* experimentation would additionally have to be experimentally analyzed *in vivo* for its ability to enzymatically degrade a phenoxy auxin herbicide and a

pyridyloxy auxin herbicide as expressed in that transgenic plant.¹⁰ Ex. 1001, Cls. 1, 32, 33, 48:62-88:14, 91:39-99:20; Silverstone, ¶¶91-93. This experimentation would require creating a new set of plant gene expression constructs, transforming and growing plant cells of interest, and expression analysis of those plants to determine which plants are producing the enzyme in sufficient quantities. Silverstone, ¶¶91-92. The selected transgenic plant strains would then need to be used to test herbicide resistance using commercially-relevant levels of phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶93. Due to the wide array of variables that could impact gene expression, protein folding, and enzyme activity, each step in the process would require the design and optimization of experimental conditions to identify variables impacting the desired activity and would need to be repeated and optimized for each amino acid sequence investigated. Silverstone, ¶¶86-93.

The '055 patent lists 12 broad categories of plants as “preferred plants” and discloses further that other types of transgenic plants “such as fruits, vegetables, ornamental plants, and trees” can be made according to the invention. Ex. 1001,

¹⁰ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9. Moreover, “surprising[.]” *in vitro* vs *in vivo* activity had been encountered in *tfdA* homologs AAD-1 and AAD-2. *Id.*, ¶10.

23:6-12. Because the independent claims do not include any limitations on transgenic plant cells of the invention, the experimentation discussed above would have to be repeated for each amino acid sequence of interest in each plant of interest. Ex. 1001, Cls. 1, 32, 33. Even dependent claim 3, which narrows the scope of claim 1 to dicotyledonous plant cells selected from the group consisting of a cotton cell, a tobacco cell, a canola cell, a soybean cell, and an *Arabidopsis* cell, requires that the experimentation aforementioned be repeated for 5 distinct species of plants. *Id.*, Cl. 3.

In fact, Patent Owner's publications and product specifications appear to contradict the function of the claimed genus. Silverstone, ¶¶52-54, 79. For example, the '055 patent throughout recites the unexpected ability of transformation with AAD-12 to confer herbicide resistance to both phenoxy and pyridyloxy auxin herbicides, yet only data for 2,4-D (a phenoxy auxin herbicide) was provided in Example 11, directed to soybeans transformed with an AAD-12 protein identical to SEQ ID NO: 2 but for the insertion of a single alanine at position 2 ("AAD-12 variant"); no pyridyloxy auxin herbicides appear to have been tested with transgenic soybeans of the invention. Ex. 1001, Abstract, 72:48-79:61; Silverstone, ¶53. Patent Owner's 2010 publication on transgenic plants expressing AAD-12 similarly, despite noting that "AAD-12 acts on pyridyloxyacetate auxin herbicides such as triclopyr and fluroxypyr," concludes

that “transgenic soybean plants expressing AAD-12 maintained field resistance to 2,4-D over five generations.” Ex. 1005, Abstract; Silverstone, ¶54. Unlike other transgenic plants in that publication, transgenic soybean was not shown to have resistance to pyridyloxy auxin herbicides. Ex. 1005, 20242; Silverstone, ¶54.

Further, the Technology Use Agreement included with Patent Owner’s Enlist E3[®] soybean product expressly prohibits the use of “any pyridine auxin herbicides (e.g., triclopyr, fluroxypyr) on emerged Enlist crops” after burndown, as seen below.

In addition to the above Prohibited Activities, and with respect to Enlist[®] herbicides, Grower acknowledges and agrees that Grower is NOT permitted to do any of the following and should Grower, or someone on Grower’s behalf, perform any of the activities listed below, shall result in Grower being in breach of this TUA:

- following burndown, use any pyridine auxin herbicides (e.g., triclopyr, fluroxypyr) on emerged Enlist[®] crops;
- following burndown, use any phenoxy auxin herbicide-containing product (e.g., containing 2,4-D, 2,4-DB, MCPA, dichlorprop, LV6, MCPB, mecoprop, which is NOT expressly labeled for use in conjunction with Enlist crops, including pre-emergent use; and/or
- following burndown, use any AOPP herbicides (e.g., quizalofop, cyhalofop, haloxyfop, diclofop, fenoxaprop, fluazifop) not expressly labeled for Enlist[®] corn on emerged Enlist corn;

Ex. 1004, 2. In the same section, Patent Owner only prohibits the use of phenoxy auxin herbicides “NOT expressly labeled for use in conjunction with Enlist crops” following burndown. *Id.* Patent Owner’s website notes that “[t]he aad-12 protein in Enlist E3 soybeans and Enlist cotton metabolizes 2,4-D choline into a non-herbicide form, thus conferring 2,4-D choline tolerance in the plant[,]” while making no mention of pyridyloxy auxin herbicide resistance. Ex. 1006; Ex. 1011, 6 (“Enlist E3 soybeans contain an AAD-12 expressing event. AAD-12 provides resistance to 2,4-D Choline Salt herbicides.”); Ex. 1012, 1 (“Enlist Duo

Herbicide,” “Active Ingredient: 2,4-D, present as choline salt... glyphosate, present as dimethylamine salt”), 11 (“Enlist soybeans contain an AAD-12 expressing event plus a glyphosate tolerance trait. These are patented genes that provide tolerance to Enlist Duo Herbicide”). Thus, Patent Owner expressly contradicts the functionality of the invention as claimed in the ’055 patent. Silverstone, ¶¶54, 81.

In order to practice the full scope of the invention claimed in the ’055 patent, would require the experimental design and cloning of an expression vector for each of the up to 2.4×10^{106} amino acid sequences within the scope of the claim, analysis of expression and *in vitro* activity for each, and further experimental analysis of expression and activity of active sequences *in vivo* in a wide range of plant species. *Id.*, Cls. 1, 32, 33; Silverstone, ¶¶80, 86-93. Where the results of such experimentation are highly unpredictable and may often produce surprising results,¹¹ such experimentation is burdensome and undue. Silverstone, ¶¶52-54, 86-93.

¹¹ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9. Moreover, “surprising[.]” *in vitro* vs *in vivo* activity had been encountered in *tfdA* homologs AAD-1 and AAD-2. *Id.*, ¶10.

(b) The '055 Patent Provides Nearly No Guidance

There is no direction or guidance provided by the specification as to which of the up to 2.4×10^{106} amino acid sequences encompassed by the claims would exhibit aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. Silverstone, ¶¶79-85. A POSITA would not find direction or guidance from the specification as to which residues, or combinations thereof, within or without the claimed “AAD-12 motif” to select for mutagenesis, or which mutations to select for those positions, without abrogating enzymatic activity. Silverstone, ¶¶79-85. The only possible “guidance” comes from the background, where Patent Owner describes previous work done on *sdpA* from *Delftia acidivorans* (SEQ ID NO: 2) and on the broad family of α -ketoglutarate dependent dioxygenases, and the Examples, in which Patent Owner tested a single amino acid sequence; a modified AAD-12 protein (SEQ ID NO: 4) “which is the same as the native SEQ ID NO:2 except for the addition of an alanine residue at the second position[,]” or, in other words, an AAD-12 protein 99.7% identical to SEQ ID NO: 2. Ex. 1001, 5:48-51, 35:11-13; Silverstone, ¶90. Although AAD-12 broadly falls within the family of α -ketoglutarate dependent dioxygenases, it is the only protein shown to possess aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. Silverstone,

¶¶48, 70. Enzymes of the α -ketoglutarate dependent dioxygenase family are known to catalyze such diverse reactions as hydroxylations, dealkylations, desaturations, epoxidations, epimerizations, halogenations, cyclizations, peroxide formations, and ring expansion/contraction reactions. Silverstone, ¶¶48. As such the only unifying features of this “guidance” are the conserved active site residues and the numbers of amino acids around and between them, as disclosed in the “AAD-12 motif.” See *id.*; see also Silverstone, ¶¶79, 84, 90.

As discussed above, enzyme function is largely a product of the tertiary structure of the protein, which forms the three-dimensional (“3-D”) structure of the enzyme as a whole and its critical active site. Silverstone, ¶¶42-44. Anything that alters the shape of an enzyme’s active site can impact the substrate specificity of the enzyme, and impact, or even abrogate entirely, its function. Silverstone, ¶¶43-44. While the conserved amino acids of the “AAD-12 motif” are necessary for the claimed activity, they are not sufficient to determine substrate specificity or activity; that depends on those amino acids (and indeed the rest of the amino acids forming the active site) being positioned in the correct spatial configuration. Silverstone, ¶¶48. As more mutations to the sequence are made, the changes in the structure of a protein will increase exponentially, further complicating any reliable prediction of the impact thereof on enzymatic function. Silverstone, ¶¶44. The ’055 patent, as described above, does not provide any guidance as to structural elements

that confer the ability to degrade both phenoxy and pyridyloxy auxin herbicides and how mutations to the sequence might impact that ability. Silverstone, ¶¶42-50, 79-85.

There is additionally no direction or guidance provided by the specification as to which of the aforementioned amino acid sequences, exhibiting aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide *in vitro*, would exhibit said activity *in vivo*. Silverstone, ¶¶79-85, 92. As noted above, the only “guidance” comes from limited studies of seven species of transgenic plants expressing a single amino acid sequence, and herbicide resistance sometimes conferred thereby. Silverstone, ¶¶53, 81, 48:62-102:49. Even among the seven species of transgenic plants tested, aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide (as shown by herbicide resistance) was not shown for all: the pyridyloxy auxin herbicide resistance of transgenic soybeans and transgenic cotton was curiously absent. Silverstone, ¶¶53, 81. Instead, the ’055 patent provides only a general guess by which a POSITA is required to further explore their own invention and experimental analysis, via trial-and-error, of endless amino acid sequences in transgenic plants of interest, not guidance by which to practice the claimed invention.

As such, the '055 patent proposes no more than a hypothesis that any protein having at least 85% sequence identity with SEQ ID NO: 2 and an “AAD-12” motif may have (and should be tested for) aryloxyalkanoate dioxygenase activity for the enzymatic degradation of both phenoxy and pyridyloxy auxin herbicides. Due to the highly unpredictable correlation between amino acid sequence and protein function,¹² combined with the highly unpredictable effects of mutations, alone or in combination, on protein tertiary structure, all amino acid sequences falling within the scope of the claims would have to be meticulously tested over a period of years for activity with both phenoxy and pyridyloxy auxin herbicides, and further for activity in each species of plants. Silverstone, ¶¶42-50, 79-85. Unquestionably, such testing is burdensome and undue. Silverstone, ¶85.

(c) The Working Examples are Limited to Only One AAD-12 Amino Acid Sequence and Seven Types of Plants Transformed to Express it

As discussed above, the experimental studies described in the '055 patent are limited to *in vitro* experiments testing a single amino acid sequence¹³ (SEQ ID

¹² As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9.

¹³ Although the '055 patent discloses the native AAD-12 protein (SEQ ID NO: 2) and prior art studying it, the working examples are limited to the AAD-12 variant comprising an alanine insertion at position 2 of the amino acid sequence (SEQ ID NO: 4), 99.7% identical to SEQ ID NO: 2.

NO: 4), and *in vivo* experiments testing some properties of the same in seven species of transgenic plants. Ex. 1001, 47:4-102:49; Silverstone, ¶¶80-82. And, as discussed above, the ability of the transgenic plants to enzymatically degrade both a phenoxy and a pyridyloxy auxin herbicide was not even described for all seven species of transgenic plants that are described (of which five are claimed).

Silverstone, ¶¶53, 81.

The '055 patent lacks data for any other amino acid sequence, lacks consistent data for the sole working amino acid sequence studied, and further lacks data for any other species of plant.

(d) The Nature of the Invention – Transgenic Plants Expressing an AAD-12 Protein for Enzymatic Degradation of Phenoxy and Pyridyloxy Auxin Herbicides

The invention is drawn to transgenic plants comprising a recombinant polynucleotide encoding an AAD-12 protein that exhibits aryloxyalkanoate dioxygenase activity for the enzymatic degradation of both phenoxy and pyridyloxy auxin herbicides. Silverstone, ¶78.

Claims 1, 3-31, and 33 only limit the AAD-12 protein by requiring that it have at least 85% sequence identity with SEQ ID NO: 2 and an “AAD-12 motif.” Silverstone, ¶78. Notably, this “AAD-12 motif” defines only a 166 amino acid stretch of the protein fixed only with respect to the identities and positions of 5 amino acids therein. Silverstone, ¶¶78-79. Claim 2 further limits the AAD-12

protein of claim 1 by requiring 90% sequence identity with SEQ ID NO: 2.

Silverstone, ¶80, fn. 1. Claim 32 includes the additional limitation that the “AAD-12 motif has 90% sequence identity with corresponding amino acids of positions 108 to 273 of SEQ ID NO: 2[,]” or, in other words, 90% sequence identity with the “AAD-12 motif” portion of SEQ ID NO:2. Silverstone, ¶80, fn. 1. Nowhere do the claims limit what mutations may be made, or, aside from the five conserved residues of the “AAD-12 motif,” where in the amino acid sequence they may be made. Silverstone, ¶¶78, 84.

The predominantly prophetic '055 specification presents the hypothesis that amino acid sequences within the broad scope of the claims could exhibit the ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides, based on *in vitro* and *in vivo* experiments using a single amino acid sequence. Silverstone, ¶¶78-80. Absent this key functional feature, *i.e.*, the ability to enzymatically degrade both phenoxy and pyridyloxy auxin herbicides, proteins of the invention would be no different from well-studied prior art α -ketoglutarate dependent dioxygenase enzymes used to impart 2,4-D herbicide resistance to transgenic plants, such as tfDa. Ex. 1001, Abstract; Silverstone, ¶¶48, 68.

(e) The Prior Art Provides Limited Guidance and Demonstrates the Unpredictability of Mutagenesis Effects on Protein Structure and Function

Although the prior art, as of March 24, 2017, identifies AAD-12 as an enzyme capable of degrading both phenoxy and pyridyloxy auxin herbicides *in vitro* and, in some plant species, *in vivo*, it also demonstrates that the wide array of activities catalyzed by the α -ketoglutarate dioxygenase superfamily of enzymes do not include other enzymes known to degrade pyridyloxy auxin herbicides.

Silverstone, ¶¶65-70. As such, it provides no guidance to a POSITA as to the key structural features of AAD-12 proteins responsible for the claimed function.

Early examples of transgenic plants for herbicide resistance in the prior art include glyphosphate-tolerant soybeans and corn, released in 1996 and 1998, respectively. Silverstone, ¶65. These two products had a very large impact on farming practices and herbicide usage, allowing general use of the inexpensive, broad-spectrum herbicide glyphosphate for both pre-planting burn downs and seasonal weed control. Silverstone, ¶65. However, this reliance on a single herbicide on greater than 90% of corn and soy acres led to the emergence of herbicide resistant weeds. Silverstone, ¶65.

Glyphosate-resistant weeds were first observed in 2000 in the United States; by 2018, there were glyphosate-resistant weeds in the majority of soybean-producing states, and farmers looked for alternative herbicides. Silverstone, ¶66.

Alternatives to glyphosphate herbicides were found in the auxin class of herbicides, which represented a very diverse set of herbicides which work by overstimulating plant cells (auxin is a growth promoting plant hormone) and causing plant death. Silverstone, ¶67. 2,4-D, a synthetic phenoxy auxin, was first used in the 1940s. Silverstone, ¶67.

The first auxin-degrading enzyme, tfdA, was identified in 1987; tfdA is in the α -ketoglutarate dioxygenase superfamily of enzymes that catalyze a wide range of reactions including hydroxylation, dealkylation, desaturation, epoxidation, epimerization, halogenation, cyclization, peroxide formation, and ring expansion/contraction reactions. Silverstone, ¶68. While work with tfdA expressed in transgenic plants demonstrated its ability to confer tolerance to 2,4-D to those plants, a negative impact on crop yield was frequently also observed. Silverstone, ¶68.

Another class of auxins includes the herbicide Dicamba, which is a benzoic acid auxin. Silverstone, ¶68. Dicamba monooxygenase (DMO) was identified from a soil bacterium as able to degrade Dicamba; however, DMO does not degrade phoxycarboxylic acid auxins. Silverstone, ¶68. DMO was engineered into soybean and corn to give another mode of herbicide tolerance. Silverstone, ¶68.

Groups working on other phenoxy auxin degrading microbes identified additional proteins that were part of the same α -ketoglutarate dioxygenase family,

but they had differing selectivity for the different auxin herbicides. Silverstone, ¶69. One of these was AAD-12. Silverstone, ¶69.

During the investigations of enzymes that degrade synthetic auxin herbicides, one enzyme was of particular interest due to the specificity of its activity. Silverstone, ¶70. Originally called sdpA and later renamed AAD-12 by Patent Owner, this enzyme was very efficient in its degradation of the phenoxy auxin herbicide 2,4-D. Silverstone, ¶70. It was then found to have significant activity on the pyridyloxy auxin herbicides triclopyr and fluroxypyr. Silverstone, ¶70. The ability to degrade two discrete classes of synthetic auxin herbicides made AAD-12 a desirable enzyme to use to engineer auxin-tolerant crops with the potential to give farmers greater flexibility in the use of synthetic auxin herbicides on their crops. Silverstone, ¶70.

The prior art demonstrates that enzyme function is largely unpredictable, even among enzymes in the same family, and despite there being the limited ability of AAD-12 to confer herbicide resistance to phenoxy and pyridyloxy auxin herbicides in some plants, the prior art does not probe or elucidate the key structural features of the enzyme responsible for its function. Silverstone, ¶¶48, 65-70. Thus, the prior art does not provide the guidance necessary to practice the claimed invention over its broad range of species.

(f) The Level of Skill in the Art is High

The level of ordinary skill in the art in the field of this purported invention is high: an ordinary skilled artisan needs specialized knowledge of protein engineering, expression, purification, and analysis, molecular cloning, genetic modification of plants, and crop science. Silverstone, ¶¶71-75.

Designing, expressing, and testing protein variants is laborious, time-consuming, complicated, and highly unpredictable due to the many effects, both direct and indirect, that a mutation can have on protein structure and function. Silverstone, ¶¶71-75. Additionally, progressing a protein variant to *in vivo* expression requires extensive work in codon optimization, transformation of target plants, and analysis of expression levels and *in vivo* efficacy.¹⁴ Silverstone, ¶¶71-75. Only one protein variant, 99.7% identical to the native SEQ ID NO: 2, had been purportedly shown to work, and that one protein variant had been purportedly shown to work in only five of the seven tested plant species. Silverstone, ¶¶53, 80-81.

¹⁴ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9. Moreover, “surprising[.]” *in vitro* vs *in vivo* activity had been encountered in *tfdA* homologs AAD-1 and AAD-2. *Id.*, ¶10.

Thus, reaching the full scope of the claimed invention would typically require a high level of skill. Silverstone, ¶71. And, while the level of skill typically required to practice in this field is already high, because of the lack of guidance in the '055 patent itself and elsewhere in the prior art, as discussed in at least §§IX.B.2(b), (d), and (e) above, such high skilled individuals may *attempt* to practice the claimed invention but *still* be left with nothing but a research idea for creating transgenic plant cells that degrade both phenoxy auxin herbicides and pyridyloxy auxin herbicides.

(g) The Study of Transgenic Plants Comprising Recombinant Polynucleotides Encoding Enzymes Conferring Herbicide Resistance is Highly Unpredictable

The field of engineering enzymes for herbicide tolerance in plants is quite complex and unpredictable, as the number of variables involved in enzyme activity, both *in vitro* and *in vivo*, is high, and activity *in vitro* often does not correlate to activity *in vivo*. Silverstone, ¶¶71-77, 80. As discussed above, for any amino acid sequence of interest, detailed biochemical analyses are required to ascertain *in vitro* whether enzymes exhibit the target functionality. Silverstone, ¶¶86-93. And although some software for the prediction of protein folding existed as of March 24, 2017, it could not accurately predict the three-dimensional structure of enzyme active sites based only on the primary sequence. Silverstone,

¶¶47, 87-88. Thus, prediction of enzyme function and substrate specificity based only on amino acid sequence was not possible. Silverstone, ¶¶87-88.

In addition, plant transformation is not completely predictable. Silverstone, ¶¶72-77. Many variables, such as the location of the transgene in the plant genome, the number of copies inserted in each strain, whether gene silencing is triggered as a result of the insertion, the proper folding and accumulation of the protein, and the particular cellular environment of the plant species can have a large impact on expression of the transgene. Silverstone, ¶¶73-74. Variation of protein expression between independently transformed plants with the same gene expression cassette has been observed often in the art, termed the ‘position effect’ because the location of the transgene in the plant’s chromosome, the ‘position’, is one of the causes of the variation and a natural result of plant transformation using *Agrobacterium tumefaciens*. Silverstone, ¶76. Additionally, off-target enzyme activities are rarely able to be predicted; they must be observed once a transgenic plant is generated. Silverstone, ¶74.

In fact, in the ‘055 patent, Patent Owner demonstrates the variability of protein expression between transgenic lines. Silverstone, ¶77. The measured protein levels of AAD-12 in transgenic soybean, as shown in Table 25 (75-78), ranged from 4.65 ng/ml to 2657.36 ng/ml among the seven events reported; a 570-fold variance in protein expression. Silverstone, ¶77. Similarly, the measured

protein levels of AAD-12 in five sample strains of transgenic canola ranged from 41.36 ng/ml to 3879.09 ng/ml; a 94-fold variance in protein expression.

Silverstone, ¶¶77.

In addition, in Patent Owner’s declaration submitted in the course of prosecution, the inventor declared, *inter alia*, that “[t]hose skilled in the art appreciate that there is a high level of unpredictability associated with expressing bacterial genes in plant systems,” such as in the case of AAD-2, which, despite having significantly higher activity with 2,4-D *in vitro* than AAD-1 (both *tfdA* homologs), “was surprisingly inactive when expressed in plants, while AAD-1 was very active.” Ex. 1010, ¶¶9-10; Silverstone, ¶¶52. It was and is well known that the field is unpredictable.

Due to the inherent unpredictability of the fields of protein engineering and the genetic modification of plants, as recognized and emphasized by Patent Owner, practicing the full scope of the invention of the ’055 patent would require a campaign of trial and error with little, if any, ability to predict the effects of mutations to the amino acid sequence of AAD-12 on the function of the enzyme, either *in vitro* or *in vivo*. Silverstone, ¶¶76-79; Ex. 1010, ¶¶9-10. As discussed above, such experimentation is burdensome and undue. Silverstone, ¶¶86-93.

(h) The Claims are Extremely Broad – Encompassing all Transgenic Plants Comprising any Recombinant Polynucleotide Encoding any AAD-12 Protein With up to 43 Amino Acid Mutations and an “AAD-12 Motif” Able to Enzymatically Degrade Both a Phenoxy and a Pyridyloxy Auxin Herbicide

The potential scope of the claims is extremely broad, covering up to 2.4×10^{106} different amino acid sequences, which sequences would need to be tested for the capability to enzymatically degrade both a phenoxy auxin herbicide and a pyridyloxy auxin herbicide. Silverstone, ¶¶79-80, fn. 1. The claims further allow for the use of those amino acid sequences in any plant. Silverstone, ¶¶78-79.

Claim 1 recites:

1. A **transgenic plant cell** comprising a recombinant polynucleotide that encodes an AAD-12 protein that exhibits aryloxyalkanoate dioxygenase activity wherein said activity enzymatically degrades a phenoxy auxin herbicide and a pyridyloxy auxin herbicide ...

Claims 1-33 cover transgenic plants transformed with a recombinant polynucleotide encoding an AAD-12 protein that enzymatically degrades a phenoxy and a pyridyloxy auxin herbicide. Only claim 3 limits the species of plants; every other claim covers all plants. As previously noted, efficacy of an AAD-12 protein *in vitro* is not predictive of its efficacy *in vivo*,¹⁵ and its efficacy in

¹⁵ As Patent Owner admits, “there is a high level of unpredictability associated with expressing bacterial genes in plant systems.” Ex. 1010, ¶9. Moreover, “surprising[.]”

one plant species is not predictive of its efficacy in all plant species. Silverstone, ¶¶52-55.

Only claims 2 and 32 further limit the sequence of the AAD-12 proteins of the invention. Claim 2 requires that the AAD-12 protein of claim 1 have an amino acid sequence at least 90% identical to SEQ ID NO: 2, and independent claim 32 requires that the “AAD-12 motif” be at least 90% identical to amino acids 108-273 of SEQ ID NO: 2. Even with these additional limitations, the numbers of amino acid sequences falling within the scope of the claimed genera include up to 10^{76} species. Silverstone, ¶¶80, fn. 1.

The claims are exceedingly broad with respect to the number of AAD-12 proteins (based on amino acid sequence, AAD-12 motif, and function) within the claimed genus and the number of plants that can be transformed therewith. Silverstone, ¶79.

in vitro vs *in vivo* activity had been encountered in tfdA homologs AAD-1 and AAD-2. *Id.*, ¶10.

X. CONCLUSION

Substantial, new, and noncumulative technical teachings have been presented for each Challenged Claim, which are lacking support and not enabled for the reasons set forth above. It is more likely than not that Petitioner will prevail as to each of these Challenged Claims. Post-grant review of claims 1-33 of the '055 is accordingly requested.

Respectfully submitted,

Dated: March 28, 2023

By: /Scott A. McKeown/
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Counsel for Petitioner Inari Agriculture, Inc.

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the Petition For Post-Grant Review complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(ii) because, exclusive of the exempted portions, it contains 12,743 words as counted by the word processing program used to prepare the paper.

Dated: March 28, 2023

By: /Scott A. McKeown/
Scott A. McKeown
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CERTIFICATE OF SERVICE

The undersigned certifies service pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(b) on Patent Owner by Priority Mail Express of a copy of this Petition for Post-Grant Review and supporting materials at the correspondence address of record for the '055 patent:

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